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EXPERT REVIEWS

Metreleptin for metabolic disorders associated with generalized or partial lipodystrophy

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Lipodystrophy is a group of acquired and inherited disorders characterized by selective loss of adipose tissue. Despite wide genotypic and phenotypic variety, many patients with lipodystrophy have similar metabolic complications including insulin resistance, diabetes mellitus, hypertriglyceridemia and hepatic steatosis. Often, these metabolic abnormalities are severe and difficult to treat with conventional glucose and lipid-lowering therapies. Lack of adipose tissue also results in marked hypoleptinemia, and there has recently been much interest in using leptin-replacement therapy to treat the metabolic complications of lipodystrophy. Administration of metreleptin, the human recombinant leptin analogue, has been shown in prospective, open-label studies to improve glucose control, dyslipidemia and steatohepatitis. This article summarizes the current evidence for the safety and efficacy of leptin-replacement therapy in patients with lipodystrophy.

KEYWORDS: diabetes mellitus • hypertriglyceridemia • insulin resistance • leptin therapy • lipodystrophy • metreleptin • steatohepatitis

Lipodystrophies are a heterogeneous group of rare, acquired and inherited disorders characterized by selective loss of adipose tissue, which may or may not be accompanied by excess fat accumulation (lipohypertrophy) in other areas. While the first reported case of lipodystrophy dates back to the late 19th century, much progress has occurred in the past decade in understanding both the molecular mechanisms of fat loss and its optimal treatment. A detailed discussion of the different lipodystrophy phenotypes, and known genetic defects causing them are beyond the scope of the current article, and interested readers are referred to several excellent reviews on this topic [1–6]. A brief summary of the classification of lipodystrophy syndromes is provided in TABLE 1.

Loss of adipose tissue can occur either due to genetic or acquired causes, and could involve either the entire body or be restricted to certain areas like the extremities, often with excess fat deposition in the unaffected areas. Based on this pattern of fat loss, both acquired and genetic lipodystrophy may be associated with either a generalized or a partial lipodystrophy phenotype. Congenital generalized lipodystrophy (CGL) is one of the most well-studied lipodystrophy syndromes, with over 300 reported cases in the literature. Affected subjects have extreme paucity of adipose tissue from birth leading to a muscular appearance, with prominent veins and an acromegaloid appearance. Subtle differences in pattern of fat loss have been recognized among the different subtypes of CGL [7], but common features include severe acanthosis nigricans, hepatosplenomegaly and early onset of diabetes, hypertriglyceridemia and steatohepatitis [8]. Marked hypoleptinemia is a universal feature of this disease [9]. Patients with familial partial lipodystrophy (FPL) have normal fat distribution at birth, but usually develop fat loss from the extremities after puberty. The most well-studied type of FPL is the Dunnigan variety (FPLD), in which fat loss from the limbs and often the trunk, especially anteriorly and over the breasts, is usually accompanied by excess fat deposition over the face and neck. Metabolic abnormalities are similar to those seen in

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Table 1. Classification and overview of different lipodystrophy syndromes.

Type	Salient features	Mode of inheritance	Genetic defects
Inherited lipodystrophies			
Congenital generalized lipodystrophy	Generalized deficiency of sc. fat from birth	Autosomal recessive	*AGPAT2, BSCL2, CAV1, PTRF, FBN1, BANF1*
Familial partial lipodystrophy	Loss of sc. fat from extremities with variable loss/excess of fat from trunk and face	Autosomal dominant (usually)	*LMNA, PPAR-G, AKT2, PLIN1, CIDEC*[†]
Lipodystrophy in association with other rare syndromes	Variable degree of fat loss in association with features of other syndromes such as MAD, SHORT, Progeria, and auto-inflammatory syndromes	Both autosomal recessive and autosomal dominant	*LMNA, ZMPSTE24, PSMB8, PIK3R1*
Acquired lipodystrophies			
Acquired generalized lipodystrophy	Development of generalized loss of sc. fat, with normal fat distribution at birth		
Acquired partial lipodystrophy	Loss of sc. fat from face, upper extremities and trunk, but not from lower extremities		
HIV-associated lipodystrophy	Loss of fat from face and limbs with variable loss/excess from trunk, and associated with antiretroviral therapy		
Localized lipodystrophy	Patchy loss of sc. fat usually following trauma or injections		

[†]Reported in a single patient with autosomal recessive inheritance.
MAD: Mandibuloacral dysplasia; sc.: Subcutaneous; SHORT: Short stature, hyperextensibility, ocular depression, Reiger anomaly, and teething delay.

CGL patients, but may not be as severe in some patients. Since the extent of fat loss is not uniform, circulating leptin levels may also vary from low to normal in these patients [9].

Acquired lipodystrophies may occur in association with other autoimmune disorders or panniculitis, or may be idiopathic [10,11]. Patients with acquired generalized lipodystrophy (AGL) may show severe metabolic complications similar to patients with CGL, while patients with acquired partial lipodystrophy (Barraquer–Simmons syndrome), who invariably have well preserved lower body fat, have lesser incidence of metabolic complications compared with other lipodystrophy syndromes. Rare forms of acquired partial lipodystrophy associated with auto-inflammatory syndromes may, however, be associated with significant metabolic abnormalities [12–14]. The most prevalent form of lipodystrophy is seen in association with HIV infection (LD-HIV), with 40–50% of patients on long-term antiretroviral therapy being affected by either generalized lipoatrophy or partial fat loss involving the face and extremities [15]. Even though the newer protease inhibitors cause less impact on body fat distribution and lipid homeostasis, LD-HIV is emerging as one of the most important challenges for long-term care of HIV-infected patients.

Despite the marked heterogeneity in etiology and clinical features of the different lipodystrophy syndromes, they share common metabolic features, whose severity may vary depending on multiple factors including age of diagnosis, lifestyle choices and modulating influence of other genes. However, often more severe complications are noted in patients with a greater extent of fat loss. This indicates the critical role of adipose tissue in maintenance of normal glucose and lipid homeostasis, and not surprisingly, adipose tissue transplantation in lipodystrophic mice has been shown to ameliorate hyperglycemia, hyperlipidemia and hepatic steatosis [16]. However, if the donor fat was obtained from *ob/ob* mice, which could not secrete leptin, no metabolic benefits were observed [17], thus highlighting the endocrine functions of adipose tissue in preventing metabolic complications. Shimomura *et al.* [18] first showed the benefit of leptin replacement therapy in lipodystrophic mice, which subsequently led to the human trials reviewed below.

Human recombinant leptin

Human recombinant leptin was first developed by Amgen, and its product, r-Met-hu-leptin (metreleptin), was used in the initial human trials studying obesity. It is now produced by Amylin Pharmaceuticals Inc., which was acquired by Bristol-Myers Squibb in August 2012. AstraZeneca has also recently acquired rights to human recombinant leptin through its partnership with Bristol-Myers Squibb. This product, now renamed as

metreleptin, is a leptin analog, and differs from native human leptin because of the presence of an additional methionine residue at the amino terminus, which does not affect its biological activity. It is available as a lyophilized powder in a vial containing 11.25 mg, which is reconstituted before it is administered as a subcutaneous injection. The usual dose to raise leptin levels in hypoleptinemic individuals to the physiological range is 0.02 mg/kg/day in adult males and 0.04 mg/kg/day in adult females. In most trials, the starting dose was 50% of this amount, and it was progressively increased to 200%, which is 0.08 mg/kg/day in female subjects, and can be administered either once or twice a day [19]. The main route of excretion is renal, and the half-life and time to maximum concentration after a subcutaneous injection is approximately 3 h [20]. Metreleptin where it was approved in March 2013 in Japan for the treatment of lipodystrophy [21]. Shionogi & Co. Ltd. has obtained a license from Amylin Pharmaceuticals for the manufacture and sale of metreleptin in Japan. In December 2013, the FDA Endocrine and Metabolic Drug Advisory Committee recommended approval of metreleptin in pediatric and adult patients with generalized lipodystrophy [22], the FDA approved metreleptin in February 2014.

Leptin replacement trials in patients with lipodystrophy

A brief summary of the different leptin therapeutic trials in patients with lipodystrophy is provided in Table 2. The first of these trials was conducted jointly by the NIH and the University of Texas Southwestern Medical Center in 2001. In this open-label, prospective, Phase II study [19], nine female patients with severe hypoleptinemia and metabolic abnormalities were treated with human recombinant leptin for 4 months. Of the nine patients, five had CGL, three had AGL and one had FPL. All patients had hypertriglyceridemia, and eight had diabetes mellitus. Treatment with twice-daily subcutaneous injections of leptin acutely increased the mean serum leptin level from 1.3 ± 0.3 to 11.1 ± 2.5 ng/ml. Marked improvement in multiple metabolic variables were noted including a nearly 2-point reduction in hemoglobin A1c, a 60% reduction in serum triglycerides and hepatic transaminases and 28% reduction in liver volume, besides improvements in glucose tolerance and insulin sensitivity. Further, leptin therapy facilitated a significant reduction in the burden of pharmacotherapy, and it was possible to reduce or completely stop glucose and lipid-lowering medications in most of the subjects. Three of the subjects who were on 800–3000 units of insulin a day at baseline were able to discontinue insulin, and three others who were on 40–700 units of insulin a day were able to substantially reduce their dose. Longitudinal follow-up of these patients for a year demonstrated the durability of leptin's beneficial effects [23]. More recently, a comprehensive review of 55 patients with different types of lipodystrophy (36 with generalized lipodystrophy and 19 with partial lipodystrophy) treated with metreleptin at the NIH has been published [24]. Analysis of treatment efficacy after up to 3 years of follow-up showed sustained reductions in glucose and triglyceride levels. The mean hemoglobin A1c reduction was over 2% and serum triglycerides declined by over 30%, with greater improvements seen in those with elevated baseline levels. Similarly, Ebihara *et al.* [25] followed seven patients with generalized lipodystrophy for 3 years in Japan, and reported not only improvements in glucose and lipid control, but also reduction in urinary albumin excretion, suggesting that long-term therapy may help reduce chronic complications. Reduction in proteinuria and hyperfiltration has also been reported in 11 of the 15 patients with generalized lipodystrophy on leptin treatment at the NIH for 4–36 months [26].

Beltrand *et al.* [27] have investigated the effect of leptin replacement therapy in children before the onset of diabetes and other serious complications. They studied seven patients with CGL, whose ages ranged from 2.4 to 13.6 years, and had hyperinsulinemia but normal glucose tolerance. Four months of metreleptin therapy improved insulin sensitivity and reduced hypertriglyceridemia and hepatic steatosis, which indicated that leptin therapy may be safe and efficacious in the pediatric age group as well. Kamran *et al.* [28] have reported an 8-year-old girl with AGL, who developed worsening of metabolic profile and arrest of pubertal development after stopping leptin therapy. Upon restarting the same, there was marked improvement in glucose and lipid levels, besides normal pubertal progression.

Leptin therapy & non-alcoholic steatohepatitis

One of the major complications of lipodystrophy is steatohepatitis, which is an important cause for morbidity and mortality in generalized lipodystrophy patients. Unfortunately, there are very limited treatment options for this, as the condition may progress despite adequate glucose and lipid control. Leptin replacement therapy has been shown to significantly improve hepatic steatosis in both generalized and partial lipodystrophy patients (Table 2). The initial studies showed significant decline in liver volume and serum levels of hepatic transaminases. Reduction in intrahepatic fat content has also been demonstrated by magnetic resonance spectroscopy [29,30]. Further, a review of a large cohort of lipodystrophy patients treated at the NIH showed significant histological improvement [31,32]. Eighty-six percent of the 50 patients showed histological evidence of non-alcoholic steatohepatitis (NASH) at baseline, while only 33% of the 27 patients, who had repeat liver biopsy after over 2 years of leptin replacement therapy, showed features of NASH [32]. There were significant improvements in steatosis grade and ballooning injury scores with a 44% reduction in mean non-alcoholic fatty liver disease activity score. Interestingly, Casey *et al.* [33] recently reported a patient with AGL who underwent liver transplantation due to NASH, but developed recurrent steatohepatitis after transplant, which resolved with leptin therapy. Leptin therapy should be strongly considered in all patients with lipodystrophy and evidence of steatohepatitis.

Table 2. Overview of leptin replacement trials in patients with lipodystrophy.

Study (year)	Design	Subjects	Duration	Change in leptin levels (ng/ml)	Beneficial effect on			Adverse effects (n)	Ref.
					Glucose metabolism	*Lipid metabolism*	*Steatohepatitis*		
Oral *et al.* (2002)	Prospective open-label	9 F (5 CGL, 3 AGL, 1 FPLD)	4 months	1.3–11.1	+++	+++	+++	Nausea/vomiting (1), hypertension/ flushing (1), streptococcal infection (1)	[19]
Lee *et al.* (2006)	Randomized crossover	7 M (LD-HIV)	4 months	1.34 to NR	+	+	–	Nil	[36]
Ebihara *et al.* (2007)	Prospective open-label	5 F + 2 M (5 CGL, 2 AGL)	36 months	1.09–18.95	+++	+++	+++	Nil	[25]
Beltrand *et al.* (2007)	Prospective open-label	6 M + 1 F (7 CGL)	4 months	0.7–24.2	+	+++	+++	ISR (1)	[27]
Mulligan *et al.* (2009)	Prospective open-label	8 M (LD-HIV)	6 months	2.7–21.3	+	++	NR	Nil	[37]
Magkos *et al.* (2011)	Double blind placebo controlled	9 M (LD-HIV)	3 months	3.7–16.5	+	–	+	ISR (1)	[38]
Chan *et al.* (2011)	Prospective open-label	44 F + 11 M (23 CGL, 13 AGL, 14 FPL, 5 APL)	≤0.5–9 years	2.75 to NR (M) 5.55 to NR (F)	+++	+++	+++	Fatigue (6) Hypoglycemia (6) Alopecia (4) Weight loss (3) ISR (2) T-cell lymphoma (2)	[24]
Sekhar *et al.* (2012)	Double-blind placebo controlled	17 M (LD-HIV)	4 months	2.64–34.35	+	+	NR	Weight loss (2), decline in $CD4^+$ T-cell count (1)	[39]
Simha *et al.* (2012)	Open-label parallel group	24 F (FPLD)	6 months	0.38–6.9 and 5.6–48.1	+	++	++	ISR (2) Hypoglycemia (1)	[34]

AGL: Acquired generalized lipodystrophy; APL: Acquired partial lipodystrophy; CGL: Congenital generalized lipodystrophy; F: Female; FPLD: Familial partial lipodystrophy, Dunnigan variety; ISR: Injection site reaction; LD-HIV: HIV-associated lipodystrophy; M: Male; NR: Not reported.

Leptin therapy in patients with partial lipodystrophy

Initial trials of leptin replacement therapy clearly showed its efficacy in patients with generalized lipodystrophy and severe hypoleptinemia. Patients with partial lipodystrophy have variable fat loss, and their leptin levels can range from low to normal. In a bid to determine whether serum leptin levels determine the response to leptin replacement therapy, we studied 24 female subjects with FPLD [34], half of whom had severe hypoleptinemia (leptin levels less than the 7th percentile), and the other half had moderate hypoleptinemia (leptin levels between 7th and 20th percentile). After 6 months of therapy, the reduction in serum and hepatic triglycerides were similar in both groups, and baseline serum leptin levels did not correlate with magnitude of response. This suggested that response to leptin replacement therapy did not depend on degree of hypoleptinemia, and it would be interesting to see if FPLD patients with normal leptin levels also respond to leptin therapy. However, it must be noted that the response to leptin therapy in FPLD patients is not as robust as in patients with generalized lipodystrophy. Serum triglycerides declined by about 15–20% only in both groups of FPLD patients, though it was much higher in those with higher baseline levels (50–60% in those with baseline serum triglyceride greater than 500 mg/dl). There was also no improvement in glycemic control, similar to the results of Park *et al.* [35], who studied six patients with FPLD. But closer examination of our data showed a significant decline in hemoglobin A1c in subjects with baseline hemoglobin A1c greater than 6.5%, and an improvement in indices of insulin sensitivity on analysis of pooled data. It would, therefore, be reasonable to conclude that leptin therapy would be beneficial for the control of hyperlipidemia, hyperglycemia and hepatic steatosis in patients with partial lipodystrophy as well as in patients with generalized lipodystrophy. Further studies are needed to examine whether leptin therapy would be beneficial in partial lipodystrophic patients without hypoleptinemia.

Leptin therapy in HIV-associated lipodystrophy

The advent of highly active antiretroviral therapy has not only greatly improved morbidity and mortality of HIV-infected patients, but has also led to the emergence of HIV-associated lipodystrophy and metabolic complications including severe dyslipidemia. The role of leptin therapy in treatment of LD-HIV is not clear. The first study to examine the benefits of leptin therapy in this population was a randomized, placebo-controlled crossover trial in seven male patients, who showed an improvement in insulin sensitivity and HDL cholesterol, but no changes in fasting plasma glucose, triglycerides or hepatic steatosis [36]. A subsequent open-label study in eight male patients did show significant improvement in dyslipidemia accompanied by decrease in fasting insulin levels [37]. However, two recent randomized, double-blind, placebo-controlled trials failed to show any improvement in fasting plasma glucose or serum triglycerides [38,39]. Both studies did show lower postprandial glucose response after leptin therapy and Sekhar *et al.* [39] reported reduction in non-HDL cholesterol without any change in lipid kinetics. Overall, it appears that leptin therapy may have favorable effects on some metabolic parameters (like hyperinsulinemia) without any adverse effects on viremia, but these responses may not be as robust as in CGL and FPLD. Further, all patients studied so far have severe hypoleptinemia (plasma leptin levels less than 3–4 ng/ml), and it needs to be determined whether LD-HIV patients with lesser degree of hypoleptinemia also benefit from leptin therapy.

Mechanisms of leptin action

There are limited studies that have examined the mechanisms by which leptin improves metabolic disturbances in patients with lipodystrophy. Weight loss has been noted in most of the studies, and is likely a result of decreased caloric intake. In our original study of leptin replacement therapy in nine patients, the self-reported mean caloric intake declined from 2680 ± 250 to 1600 ± 150 kcal/day [19]. There was a concomitant decrease in energy expenditure from 1920 ± 150 to 1580 ± 80 kcal/day, unlike earlier animal studies, which had shown an increase in energy expenditure with leptin replacement. McDuffie *et al.* [40] observed significant improvement in measures of satiety and decrease in food intake under test conditions after leptin therapy. Using functional MRI, Aotani *et al.* [41] have recently shown that leptin therapy helps to suppress postprandial neuronal activity in certain brain areas, which can lead to improved satiety. All this clearly suggests that leptin has a strong influence on the central regulation of feeding, and this might be an important contributor to its metabolic effects. Whether it also exerts a peripheral anti-steatotic effect, as postulated by some investigators [42], needs further study. We [29] and other investigators [30] have reported significant decline in intrahepatic and intramyocellular lipid content following leptin therapy. However, whether these reductions in hepatic and muscle steatosis are secondary to decreased caloric intake and weight loss, or due to a direct effect on fatty acid oxidation in non-adipose tissue, cannot be determined from these studies. Based on recent experimental data in lipodystrophic mice, which showed that increase in 5′-AMP activated protein kinase activity in liver and skeletal muscle after leptin treatment [43], it is likely that leptin exerts its effects by both central and peripheral mechanisms, the relative importance of each needs to be determined by future controlled experiments.

Adverse effects of leptin therapy

Therapy with metreleptin has generally been reported to be very well tolerated with few adverse effects (Table 2). The most common side effect noted was injection site reactions, which were mild, transient and did not require any intervention. Weight loss, including significant decline in lean body mass, has also been noted [44]. Other reported side effects are likely related to the disease or its treatment such as hypertriglyceridemic pancreatitis, progression of liver and kidney disease and hypoglycemia. Most other side effects were felt by the investigators to be not related to the study medication. Two patients with AGL have been reported to develop T-cell lymphoma

during leptin replacement therapy [24]. Though both patients had abnormal bone marrow biopsy at baseline, it would be prudent to follow patients at risk for neoplastic or autoimmune disorders carefully, as leptin could potentially have immunomodulatory effects [45]. Another 13-year-old patient with AGL who had no prior hematological disease also developed T-cell lymphoma when on metreleptin therapy [46]. A common finding after prolonged leptin therapy is the development of leptin antibodies. Both neutralizing [47] and non-neutralizing [25] antibodies have been reported, and may underlie some cases of apparent resistance or poor response to leptin therapy [47]. It is also possible that development of neutralizing antibodies might not only diminish the therapeutic effect of exogenous leptin, but may also worsen underlying metabolic abnormalities by blocking the effects of endogenous leptin in those patients without severe hypoleptinemia. Interestingly, Amylin Pharmaceuticals and Takeda Pharmaceutical Co. Ltd. discontinued the development of metreleptin for treatment of obesity due to the development of leptin antibodies in patients treated with metreleptin.

Conclusion

Lipodystrophies are a rare group of heterogeneous disorders characterized by similar metabolic complications related to severe insulin resistance. While some patients with lipodystrophy can be effectively managed with traditional glucose and lipid-lowering medications, these measures are not sufficient in many others with severe insulin resistance and hypertriglyceridemia. Human recombinant leptin therapy has been shown to cause marked reduction in glucose and lipid levels, besides improving hepatic steatosis in patients with generalized lipodystrophy and hypoleptinemia. Similar, but slightly less robust improvement has been noted in patients with partial lipodystrophy, while only some aspects of the disease seem to be favorably affected in patients with HIV-associated lipodystrophy. More randomized controlled trials are necessary to firmly establish the role of leptin therapy in patients with different types of lipodystrophy, but given the rarity of these disorders, this may be a difficult undertaking. Current evidence appears to clearly suggest that leptin replacement therapy in hypoleptinemic (leptin levels less than the 20th percentile of age- and sex-matched subjects) patients with lipodystrophy is both safe and efficacious.

Expert commentary

Despite the limitations of an open-label study, the available evidence strongly supports use of leptin therapy to ameliorate the metabolic abnormalities associated with lipodystrophy. While a placebo effect cannot be excluded, the magnitude of glucose and triglyceride reduction despite cessation of glucose and lipid-lowering therapy, is suggestive of a true biological effect. Further, short-term discontinuation of leptin therapy was noted to cause elevation in glucose and triglyceride levels, despite no change in diet or concomitant medications, which were promptly reversed by reinstitution of leptin therapy [19]. The lack of data from controlled trials should not preclude the use of this medication in patients with rare lipodystrophy disorders, for which limited therapeutic options currently exist. This is especially true for patients with generalized lipodystrophies, both congenital and acquired, who have severe hypoleptinemia. Similarly, patients with partial lipodystrophy may also derive benefit irrespective of leptin levels, though trials in FPLD patients with normal leptin levels need to be performed. In general, patients with more severe lipodystrophy, and with more severe metabolic abnormalities, seem to derive the greatest benefit, and would be ideal candidates for leptin replacement therapy. Also, given the marked histological improvement, patients with lipodystrophy and NASH should be strongly considered for metreleptin therapy. Since HIV-associated lipodystrophy is not uncommon, and early studies have shown conflicting results, larger, long-term studies are needed in this patient population before leptin therapy can be advocated. Future studies should also focus on mechanisms of leptin action in patients with lipodystrophy, as this may also offer clues to effective treatment of diabetes, dyslipidemia and NASH in patients with obesity and metabolic syndrome.

Five-year view

It is very likely that in the coming few years, leptin replacement therapy will be the treatment of choice for patients with generalized lipodystrophy, and will be a useful adjunct in treating patients with partial lipodystrophy who have significant metabolic abnormalities, while it is unlikely to be of uniform benefit in patients with LD-HIV. An interesting anticipated development would be its use in 'non-syndromic' lipodystrophies, in other words, patients with upper body obesity who have significant hypertriglyceridemia and steatohepatitis. While it may not be of much benefit in reducing blood sugars in patients other than those with generalized lipodystrophy, its 'anti-steatotic' effect may prove to be beneficial in the treatment of NASH in patients with different types of lipodystrophy, and perhaps also in those with disproportionate upper body obesity. However, it is important to determine if development of leptin antibodies will affect long-term efficacy of leptin replacement therapy.

Disclaimer

This article has been amended to reflect the recent FDA approval of metreleptin.

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The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Key issues

- Lipodystrophies are a group of heterogeneous acquired and inherited disorders characterized by selective loss of adipose tissue.
- Patients with lipodystrophy have common metabolic abnormalities related to insulin resistance such as diabetes mellitus, hypertriglyceridemia and steatohepatitis, which are sometimes difficult to treat with conventional glucose and lipid-lowering therapies.
- Metreleptin, a human recombinant leptin analog, has been shown in open-label trials to cause significant reduction in glucose and lipid levels, besides histological improvement in non-alcoholic steatohepatitis, in patients with lipodystrophy and hypoleptinemia.
- Patients with generalized lipodystrophy and those with severe metabolic abnormalities show more robust response to leptin replacement therapy.
- There is concern about development of leptin antibodies in those treated with metreleptin, which can potentially limit long-term efficacy. Development of hematological malignancies such as T-cell lymphoma has been noted in three patients on metreleptin therapy.
- The benefit of leptin therapy in patients with HIV-associated lipodystrophy is not clearly established.
- Metreleptin therapy was approved for clinical use by the US FDA in February 2014.

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